TABLE 15

Summary of Naproxen Pharmacokinetic Parameters by Study Day and Dose Time for Treatment D (EC E20 + Naproxen)

Day	Dose Time	Statistics	C_{max} (μg/mL)	t_{max} (hr)	AUC_{0-t} (hr*μg/mL)	$AUC_{0-10,am}$ or $AUC_{0-14,pm}$ (hr*μg/mL)	AUC_{0-24} (hr*μg/mL)	$t_{1/2}$ (hr)
1	AM	Mean	65.5		409	409		8.85[a]
	n = 28	% CV	25		16	16		22
		Median	67.0	1.50	411	411		8.44
		Min	39.9	0.75	293	293		6.17
		Max	113	6.00	562	562		14.1
1	PM	Mean	81.5		685	685	1094	15.4
	n = 28	% CV	14		10	10	12	31
		Median	80.8	1.50	662	662	1068	14.7
		Min	58.2	0.50	592	592	909	9.04
		Max	107	2.50	855	855	1398	32.8
9	AM	Mean	90.0		617	617		9.32
	n = 28	% CV	19		12	12		23
		Median	87.0	1.50	619	619		9.39
		Min	59.4	0.50	493	493		5.77
		Max	126	4.00	793	793		15.4
9	PM	Mean	86.5		769	769	1387	14.4
	n = 28	% CV	13		10	10	10	17
		Median	89.6	1.50	760	760	1371	14.7
		Min	67.3	0.75	619	619	1130	10.5
		Max	123	4.00	930	930	1723	21.1

[a]n = 27.

Drug Concentrations or Pharmacokinetics in Relation to Pharmacodynamic Measurements

As shown in FIG. **7**, the relationship between the mean total plasma exposure to esomeprazole, i.e., AUC_{0-24} on Day 9 (representing steady-state exposure), and the mean percent time with intragastric pH>4.0 on Day 9 (the primary PD endpoint) can be described by a typical pharmacological maximal response (E_{max}) model defined below:

$$\text{Effect}=(E_{max}*AUC_{0-24})/(EC50+AUC_{0-24}),$$

where

Effect=Mean percent time intragastric pH>4.0 on Day 9 (assuming zero time intragastric pH>4.0 when esomeprazole AUC_{0-24} equals zero)

E_{max}=Maximal Effect

EC50=Plasma mean AUC_{0-24} required to produce 50% of the Maximal Effect

The E_{max} was estimated to be 90.4% of time with intragastric pH>4.0 over the daily interval at steady state. The AUC_{0-24} value required to achieve half (or 50%) of the maximal response was estimated to be 713 hr*ng/mL. Following PN 400/E20, the PD response had achieved about 80% of the maximal response, which was only slightly less than that (85% of E_{max}) achieved by PN 400/E30.

Repeat doses of PN 400/E30 and PN 400/E20 resulted in faster onset of increased intragastric pH (at about 1 hour post dose) than EC E20+naproxen, which was at about 1.5 hours post-dose (FIG. **1**).

As shown in the FIG. **8**A, the release of naproxen from PN 400 occurred 1.5 to 2 hours post AM dose. Before naproxen was absorbed to peak concentrations following PN 400 treatment, intragastric pH had already achieved high levels, well above pH 4.0 (FIG. **8**A). In fact, with the BID regimen of PN 400/E20, given 1 hour before a meal, the intragastric pH was maintained at above 4.0 for greater than 70% of time over a 24-hour period, which would encompass any rise in plasma naproxen concentrations throughout the day.

In contrast, EC E20+naproxen produced peak naproxen concentrations that preceded the increase in intragastric pH (FIG. **8**B). In fact, peak naproxen concentrations occurred 1 to 2 hours post dose, which coincided with the time period when intragastric pH was lowest (FIG. **8**B).

What is claimed is:

1. A method for delivering a pharmaceutical composition to a patient in need thereof, comprising:

orally administering to the patient an AM unit dose form and, 10 hours (±20%) later, a PM unit dose form, wherein:

the AM and PM unit dose forms each comprises:

i) naproxen, or a pharmaceutically acceptable salt thereof, in an amount to provide 500 mg of naproxen, and

ii) esomeprazole, or a pharmaceutically acceptable salt thereof, in an amount to provide 20 mg of esomeprazole;

said esomeprazole, or pharmaceutically acceptable salt thereof, is released from said AM and PM unit dose forms at a pH of 0 or greater,

the AM and PM unit dose forms target:

i) a pharmacokinetic (pk) profile for naproxen where:

a) for the AM dose of naproxen, the mean C_{max} is 86.2 μg/mL (±20%) and the median T_{max} is 3.0 hours (±20%); and

b) for the PM dose of naproxen, the mean C_{max} is 76.8 μg/mL (±20%) and the median T_{max} is 10 hours (±20%); and

ii) a pharmacokinetic (pk) profile for esomeprazole where:

a) for the AM dose of esomeprazole, the mean area under the plasma concentration-time curve from when the AM dose is administered to 10 hours (±20%) after the AM dose is administered (AUC0-10,am) is 1216 hr*ng/mL (±20%),

b) for the PM dose of esomeprazole, the mean area under the plasma concentration-time curve from when the PM dose is administered to 14 hours (±20%) after the PM dose is administered (AUC0-14,pm) is 919 hr*ng/mL (±20%), and